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ACCE and Genomic Testing

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Scope

• Focus on molecular assays, attempting to fit models/definitions developed for clinical chemistry

• Disclaimer: My own opinions, considering BCBSA policy, but also looking towards the future
ACCE Framework

- **Analytical validity:**
- **Clinical Validity**
- **Clinical Utility**
- **Ethical, legal, social implications**

**Purposes for tests**
- Reduce morbidity/mortality
  - Provide information to manage patient/family members
  - Assist with reproductive decision-making

Framework Comparisons

Matchar Chapter 1. Introduction to methods guide for medical test reviews. JGenIntmed 2012
BioMarkers vs Mutations

• Molecular Biomarkers (associated, relative risks)
  – Clinical trials to establish association
  – More likely to be proprietary
    • GWAS studies
    • Expression patterns

• Pathogenic variants (causative)
  – Mendelian disorders (germline)
  – Oncology (somatic variants)
    • Driver mutations, therapy – drug susceptibility, resistance variants
Analytical Validity

• Does the assay detect what is claimed that it detects?
  – Accuracy/precision studies
    • Determines analytical sensitivity and specificity
  – Region interrogated defined
    • Targeted mutations
    • Gene sequencing
      – Targeted exons, Full gene sequencing (all exons, intron/exon boundaries, some known deep intronic or regulatory mutations
    • Deletion/duplication analysis
  – Performance affected by
    • Interfering substances (well known)
    • Rare, unknown variants at primer/probe sites, creating 2º structure
    • Mosaicism, low mutation levels, limits of detection
  – Continuing evaluation: proficiency testing/alternative assessment
Clinical Validity

• Does the test correctly identify affected/unaffected individuals?
  – Does Analyte (gene) or Assay determine clinical validity?
    • Do mutations in a gene cause disease?
      – Linkage studies, functional analysis, case/control, cloned from known protein sequence
    • Depends on the region interrogated /defined phenotype
      – Clinical sensitivities (F8 example)
      – Not necessarily method dependent
  – PPV/NPV a measure of analytic or clinical validity or clinical utility?
    • How is it defined for single gene disorders?
      – Penetrance, mild vs severe mutations?
    • Dependent on population, indication for testing
Clinical Validity - Complications

• Inherited disease concepts
  – **Penetrance/expressivity**
  – Pleiotropy – single gene influences multiple traits
  – **Clinical Overlap:** pathogenic variants in multiple genes cause similar phenotypes
  – **Phenocopy** – phenotype overlap due to environment that resembles the effect of inherited pathogenic variants
    • Carefully define “phenotype”, (BRCA Example)
  – Polygenic traits: multiple genes contribute to the phenotype
  – **Same test for diagnostic, predictive, carrier testing**
  – Interrogating regions (deep intronic, regulatory) of a gene or genes not well understood will produce more Variants of Uncertain Significance (VUS)
  – All genes on a panel to have established clinical validity
  – ClinGen project funded by NIH to examine disease categories
Modified ACCE (Fryback-Thornbury) for Clinical Utility

• Diagnostic Thinking Efficacy (Diagnosis):
  – Rule out disease (differential diagnosis)
  – Stop diagnostic odyssey: prevent additional testing
  – Appropriate follow-up/monitoring

• Therapeutic efficacy
  – Drug response

• Patient outcome efficacy
  – Patient management: improve outcomes
  – Prognostic: Determine aggressiveness of disease/treatment
  – Predictive: pre-symptomatic, familial mutations, reproductive

• Societal efficacy:
  – Proper use of medical/community resources
Reasons to Show Utility

• Aid clinicians in ordering, interpreting
• Demonstrate value of genomic medicine
• Reimbursement
Definition of Clinical Utility

• Utility for patient, clinician, payers, regulators, society

• Definition of Clinical Utility
  – Narrow: Determine drug and dose – improved outcomes demonstrated
  – For clinician/patient: diagnosis, treatment, management
    • Inherent utility of diagnostic testing
  – For patient/family: predictive testing, reproductive planning, long term care planning
  – For Payers: treatment, improved outcomes
  – For Regulators: analytical and clinical validity, expand to utility?
  – For Society: Efficient use of healthcare/community resources
Establishing Clinical Utility

- Randomized prospective controlled studies
- Retrospective studies
  - Archived samples
- Issues with:
  - Rare inherited diseases
  - Rare mutations (somatic)
  - Long duration
  - Ethically valid?
  - Inconclusive results
    - Poorly designed
    - Insufficient numbers
EGAPP

• **Evaluation of Genomic Applications in Practice and Prevention**

• Common conclusion
  – Insufficient evidence
    • ...found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression.
    • In the absence of supporting evidence..., EGAPP discourages the use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed

• Taken as “Evidence Against”
  – SSRI studies extended to other uses

• Re-evaluate with continuing studies

http://www.egappreviews.org/
Circular Problem

Lower evidence  →  Marker utility poorly valued

Lack of clinical trials  →  Not reimbursed

Lower funding/lack of interest  →  Lower evidence

Testing Symptomatic Individuals

• Diagnostic:
  – Explain the clinical symptoms
  – Understand disease course

• Prognostic:
  – Understand likely disease progression
  – Preventive management

• Therapeutic:
  – Determine most effective treatment/management
Asymptomatic Individual

• Predictive testing
• Family history
• Known familial mutations
  – Test affected individual for the benefit of family members
• Population screening
  – Newborn screening (State programs)
Testing Cancer Cells (Somatic)

• Diagnostic: identify genetic abnormalities causative of or resulting from disease
• Prognostic: determine aggressiveness of disease/treatment
• Predictive: determine therapy, resistance to therapy
Models

• Fully powered clinical studies not always feasible
  – Underpowered or partial data modeled for useful information?
• Require models for different scenarios? Types
  – Oncology
    • Chain of evidences (biological relationships/pathways)
    • Demonstrative usefulness in one or multiple cancer/specimen types?
    • Define “supportive” and “adequate” evidence
  – Inherited diseases
    • Approximately 4600 known medically relevant genes
      – Show each disease separately?
      – Another 20,000 in genome – how many will be shown to be medically relevant?
    • Compare to non-molecular diagnostic pathway/procedures
    • Diagnostic efficacy
• Same assay used for different purposes
Clinical Utility for Oncology

• “Driver” mutations essential for tumor progression
• “Passenger” mutations that might facilitate, but not essential for progression
• Prognosis
  – Help determine aggressiveness of treatment
• Predictive testing for therapy
  – Multiple tumor types – *BRAF* V600E
  – Histologically identical tumors - *KRAS2*
<table>
<thead>
<tr>
<th>CONDITION</th>
<th>DIAGNOSIS</th>
<th>MANAGEMENT</th>
<th>PROGNOSIS</th>
<th>PREDICTIVE</th>
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<tbody>
<tr>
<td>Acute myeloid leukemia</td>
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<tr>
<td>Stem cell transplant monitoring</td>
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<td>Chronic lymphocytic leukemia</td>
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<td>Chronic myelogenous leukemia</td>
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<td>Colon Cancer</td>
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<td>Breast and ovarian cancer</td>
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<tr>
<td>Non-small cell lung cancer</td>
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<td>Acute promyelocytic leukemia t(15;17)</td>
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<td>Gastrointestinal Stromal Tumors</td>
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<td>Melanoma</td>
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Clinical Utility for Inherited Diseases

• Many are rare:
  – Approximately 4600 known human genetic disorders
  – Not feasible to show utility for each one
  – Aggregate by disease type, test method?
  – Still may have strong clinical validity/utility
    • lack cpt codes
  – Together, they are substantive
    • 100% of individuals have genetic variants that could affect drug response
## Selected Molecular Tests with Tier 1 cpt

### Genetics

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>DIAGNOSIS</th>
<th>MANAGEMENT</th>
<th>PROGNOSIS</th>
<th>PREDICTIVE</th>
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<td>Alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease</td>
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<td>Alpha-1-antitrypsin deficiency</td>
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<td>Ashkenazi Jewish:</td>
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<td>Bloom syndrome</td>
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<td>Canavan disease</td>
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<td>Cystic Fibrosis</td>
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<tr>
<td>Cytogenomic constitutional abnormalities (e.g. Kleinfelter, trisomy 21)</td>
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<td>Familial adenomatosis polyposis (FAP)</td>
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<td>Fragile X</td>
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<td>Huntington Disease</td>
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<td>Hereditary breast and ovarian cancer</td>
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<td>Hereditary hemochromatosis</td>
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<td>Limited</td>
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<tr>
<td>Hereditary non-polyposis colorectal cancer, Lynch syndrome</td>
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<td>Long QT syndrome</td>
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<td>Marfan syndrome</td>
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<td>Nonsyndromic hearing loss</td>
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<td>Rett syndrome</td>
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<tr>
<td>Spinal Muscular Atrophy</td>
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</table>
Example: Hereditary Hemorrhagic Telangiectasia

• Appropriate use of health resources
  – Life threatening cerebral/pulmonary manifestations
    • Brain MRI with contrast:
    • Contrast echocardiogram:
      – 20% need F/U of chest CT, radiation exposure
  – Surveillance: every 5 years in affected individuals, or in unaffected individuals until approximately age 40 (unless ruled out by molecular testing)
  – Guidelines available
    • Faughnan J Med Genet 2011;48:73e87

Pictures courtesy of Whitney Wooderchak-Donahue
Single Gene vs Gene Panel

• ASHG:
  – “…, the scope of genetic testing should be limited to single-gene analysis or targeted gene panels based on the clinical presentation of the patient....”
    – Botkin JR et al. Points to consider: Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. ASHG 2015;97:6-21

• Use most focused assay available (as appropriate)
  – Single gene, if meets clinical criteria
  – Small gene panel improves diagnostic yield, if non-classic phenotype
  – Large gene panels - common symptoms for numerous diseases, in place of an exome?
  – Exome/genome for combination of symptoms/family history consistent with genetic etiology, but remains undiagnosed
**Marfan syndrome**
- Tall stature
- Arachnodactyly
- Hypermobile joints
- Scoliosis
- Aortic aneurysm
- Learning disability
- Positive family history, sudden death in a close relative

**Loeys-Dietz Syndrome**
- Arterial tortuosity
- Hypertelorism
- Bifid (split) or broad uvula
- Aneurysms
- Scoliosis
- Positive family history, sudden death in a close relative

**Ehler Danlos Syndrome Type IV**
- Aneurysm
- Thin, translucent skin
- Extensive bruising
- Hypermobility
- Clubfoot
- Spontaneous pneumothorax
- or haemothorax
- Positive family history, sudden death in a close relative

**Arterial Tortuosity**
- Tortuosity, elongation, and aneurysms of major arteries and the aorta
- Aortic stenosis, pulmonary artery or pulmonary valve
- Hypertelorism
- Hypermobile joints
- Arachnodactyly
- Scoliosis
- Hyperextensible skin
- Positive family history, sudden death in a close relative

Courtesy of Dr. P Bayrak-Toydemir
Marfan Single Gene Assay

- 66 exons
- Mutation positive (~10% positivity rate)
  - Includes known pathogenic and suspected pathogenic
  - 56%: diagnosis based on clinical phenotype
  - 44%: suspected diagnosis of Marfan disease
- ~4% Variants of uncertain clinical significance
  - 64%: suspected diagnosis of Marfan
  - 37%: diagnosis based on clinical phenotype

p. Arg545Cys
Clinical Sensitivity of Gene Panel

• Aortopathy panel:
  – 17 genes
  – Each has clinical validity/utility separately
  – Clinical sensitivity: approximately 20%
    (doubled)
  • Internal data from Dr. P Bayrak-Toydemir
Looking towards the Future: Exome Diagnostic Yield

• Overall
  – 25%

• Severe Intellectual Disability: 16%

• Neurological diseases: 64%
  • Brain. 2015 Feb;138(Pt 2):276-83.

• Retinal dystrophies: >50%
  • Am J Opthal online April 2015 doi:10.1016/j.ajo.2015.04.026
Levels of Evidence

• Multiple models needed
  – Randomized control studies
  – Retrospective
  – Adaptive clinical trials
  – Diagnostic yield
  – Observational data
  – Linkage
  – Functional studies
  – Biological relationships/pathways
  – Current care vs molecular diagnostic models
  – Professional organization practice guidelines
Thanks to:

• AMP’s Committees
  – Professional Relations
    • FEND working group
  – Clinical Practice
  – Economic Affairs

• ARUP Molecular Genetics/Genomics
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